VCIP Induces Cell-Cell Interactions: Its Role In Angiogenesis

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Angiogenesis is not only required for normal physiology, but is also vital for many diseases that depend upon growth of blood vessels including growth of solid tumors, diabetic retinopathy, and cardiovascular diseases. Endothelial cells (ECs) that line the blood vessels play direct role in the formation of new blood vessels. Upon activation ECs elongate extensively and form cell-cell interactions, the molecules and mechanisms that control these events are not entirely understood. By employing subtractive suppression hybridization and differential display technique, we identified and cloned an induced gene from ECs undergoing capillary morphogenesis that we named as VCIP for VEGF & type I Collagen Inducible Protein. Herein, we demonstrate that endogenous and recombinant VCIP proteins are expressed as N-glycosylated and non-glycosylated forms of ~38 and 46/48 kDa molecular masses. Immunofluorescent localization and cell surface biotinylation followed by immunoprecipitation assay show that VCIP is a cell surface protein. Encouraged by its atypical membrane anchoring structure we hypothesized that VCIP can induce and organize both homotypic and heterotypic cell-cell interactions. In support of this hypothesis, the overexpression of wild-type but not mutant-VCIP promoted cell-cell interactions. In addition, we found that recombinantly expressed VCIP interacted productively with a subset of integrins on ECs, this data was further supported by solid-phase ELISA assay. Intriguingly, immunoprecipitation and Western blot analyses suggested that VCIP collaborates with signaling molecules to activate intracellular signaling machinery that includes tyrosine phosphorylation of Fak and Shc, molecules required for EC migration and differentiation. Importantly, immunostaining data showed that VCIP was strongly coexpressed with VEGF, MMP2, and avb3 integrin in tumor vasculature including angioma, hemangioma, and melanoma. Based upon our collective results we propose that VCIP nucleates a unique cell-cell interaction, a process necessary for normal and pathological angiogenesis.